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A Model of the Stress-Induced Activation of Prefrontal Cortical Dopamine Systems

Coping and the Development of Post-Traumatic Stress Disorder

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The physiological and behavioral responses called stress are of critical importance to the survival of the organism. These integrated responses are homeostatic adaptive strategies, ranging from changes in metabolism (e.g., the steroid-induced shift to glycogenolysis) to more complex behaviors. These changes have the common goal of reducing exposure to a stressor or reducing the traumatic effects of a stressor.

Since the stress response is critical to the survival of an organism, it is reasonable to posit that there should be some redundancy in the neurochemical mechanisms and neuroanatomical substrates that comprise the central stress systems. As can be rather easily seen from perusal of the chapters in the first section of this volume, virtually every neurotransmitter can be shown to respond to stress. However, while most transmitters respond to stress, the central sites at which these changes occur are relatively restricted. In particular, the prefrontal cortex (PFC) appears to be a site at which changes in many transmitter systems are observed. Thus, the release and metabolism of specific afferents to the PFC, including dopaminergic, noradrenergic, serotonergic, and cholinergic neurons, are increased by exposure to stressors. The activities of interneurons and projection (pyramidal) neurons in the PFC are in turn altered by the changes in the afferents impinging on the interneurons. Thus, the function and release of γ-aminobutyric acid (GABA) and various neuropeptides (in interneurons) and excitatory amino acids (present in pyramidal cells and afferent fibers) are altered by stress.

The dopaminergic innervation of the PFC is remarkably sensitive to stress. First described a generation ago (1), prefrontal cortical dopamine (DA) afferents sharply increase metabolism and release of DA in response to very mild stressors (1,2). In fact, the PFC is unique in that a large body of literature has revealed that virtually all of the factors thought to be involved in the development of posttraumatic stress disorder (PTSD) can be shown to influence or regulate the response of the PFC dopaminergic neurons. These factors range from genetic and early perinatal events hypothesized to be related to the development of PTSD (see Chapter 23), to the changes incentral noradrenergic (see Chapter 3), serotonergic, cholinergic, and peptidergic neurons (see Chapter 6), to the relationship of the cortical

dopaminergic system, and to drugs of abuse, including psychostimulants and ethanol (see Chapter 5). Moveover, the PFC has widespread efferents (3), including direct projections to spinal cord vasomotor centers (4), and projections to the hypothalamus and critical brainstem autonomic regions as well as to such regions as the amygdala and hypothalamus (see Chapter 1) that allow the PFC to participate in the coordinated responses to stressors.

In many ways, the cortical DA response to stress can be considered a microcosm of the central changes thought to occur in PTSD. We will briefly review regulation of the DA neurons that innervate the PFC, present a model for the genesis of the stress-induced increase in PFC DA release, and attempt to relate the function of dopaminergic regulation of PFC neurons to a more widespread network of sites (including the amygdala) that are functionally coupled in stress. As befits a topic as broad as stress, there is some redundancy in this volume's coverage of the PFC DA response to stress (see Chapters 4 and 5). We will discuss the PFC in relation to a more widespread stress "system" that involves the amygdala (see Chapters 7 and 11). We will also try to minimize the redundancy with other contributions to this volume, and refer readers to these other chapters for more detailed descriptions of certain aspects of the stress response.

ANATOMY AND PHYSIOLOGY OF THE PREFRONTAL CORTICAL DOPAMINE INNERVATIONS

Anatomical Organization of Cortical Dopamine Afferents

Dopamine afferents to the PFC are present in all mammals. The original observation of a cortical DA innervation was made in the rat (5). In this species, DA fibers discretely innervate the medial and sulcal (suprarhinal) prefrontal cortices, but are not observed in other cortical regions rostral to the genu of the corpus callosum (6.7). There are also relatively minor dopaminergic innervations of the posterior cingulate and suprarhinal cortices, pyriform cortex, and entorhinal cortex (6,7). In contrast to the localized distribution of cortical DA axons in the rat, there is a much more widespread dopaminergic innervation of the cerebral cortex in primate species, with DA projections found in a variety of sites, including association, motor, and sensory cortices (8.9).

In all species examined, the DA innervations of the cortex originate solely from neurons in the ventral mesencephalon. In the rodent, the cortical DA innervations are derived from neurons in the ventral tegmental area of Tsai (VTA; A10 cell group), with a small number of neurons in the substantia nigra (SN; A9 cell group) and retrorubral field (RRF; A8 cell group) projecting to the PFC and to the more lateral (suprarhinal, pyriform, and entorhinal) cortices (8–11). In primate species the DA innervation of the cortex, including the dorsolateral PFC, appears to be derived predominantly from DA neurons in the SN and RRF, with a smaller contribution of VTA DA neurons than would be expected on the basis of the rodent data (12.13).

Certain DA neurons that project to forebrain targets contain, in addition to DA, a number of neuropeptides, including neurotensin and cholecystokinin (see Chapter 6). We have recently reviewed the anatomy and functional attributes of colocalization in DA neurons (14).

The midbrain DA cell body regions receive afferents from a large number of sources (15.16). Particularly prominent are those arising from the PFC, ventral pallidum, lateral hypothalamus, and dorsal raphe region. Since stressors must gain access to the midbrain in order to activate the DA neurons that project to the PFC, it is apparent that afferents to the VTA have been among the most intensely studied of the regulatory features that govern the activity of forebrain DA innervations (17); the reader is referred to reviews by Deutch and Roth (2) and Kalivas (16) for extended discussions of these afferents.

DA axons in the PFC contact both pyramidal cells and interneurons. It was originally thought that the actions of DA in the PFC were paracrine in nature. Although contacts between DA neu-

rons and pyramidal cells in the **PFC** were evident, these contacts did not display the typical pre- and postsynaptic thickenings that are the electron microscopic hallmark of synapses (18). However, it was subsequently shown in serial reconstructions that DA axons form very small symmetric synapses with **PFC** pyramidal cells (19–22). Paradoxically, recent ultrastructural data suggest that D_1 DA receptor-like immunoreactivity is not present at the point where DA axons form synapses with pyramidal cells (23), again harkening to a paracrine mode of action (at least with regard to the D_1 receptor-like protein revealed by immunohistochemistry). In addition to DA afferents synapsing onto pyramidal neurons, recent data indicate that DA axons contact and synapse with certain GABAergic interneurons (24–26).

The DA axons that form synapses with pyramidal cells are frequently part of a triadic arrangement, with both an asymmetric (excitatory) input and the inhibitory DA axon contacting the same pyramidal cell (21). The source of the excitatory (presumably glutamatergic) axon is not known. The glutamatergic contribution to the triad could conceivably originate from the medial thalamus (27,28), basolateral amygdala (29), other cortical regions, and possibly the VTA (30); a recent preliminary report indicates that the hippocampal projections to the **PFC** are not the source of the excitatory part of the triad (31). Since DA appears to have a modulatory role in the **PFC** (see next section), the source of the excitatory input with which DA shares a pyramidal cell target may be of crucial importance, dictating in part when DA afferents to the cortex are activated.

Physiology of the Cortical Dopaminergic Systems

Dopamine inputs to the **PFC** inhibit the activity of pyramidal cells in vivo (32–34). The dopaminergic inhibition of cortical output neurons appears to depend upon an atypical D_2-like receptor (33,35). In sharp contrast to a large body of data indicating that DA inhibits **PFC** pyramidal cells (including an intracellular in vivo study [36]), an in vitro study indicates that DA induces a very small (2–3 mV) depolarization and that high concentrations of DA increase the number of spikes evoked by a single depolarizing pulse (37). These data are most parsimoniously explained by DA increasing the input resistance of the cell, therefore suggesting a modulatory role for DA.

The proposed modulatory role for DA in the **PFC** offers a reasonable reconciliation between the observed DA-elicited inhibition of pyramidal cells in vivo and the different electrophysiological effects observed in vitro. Under in vitro conditions, pyramidal cells are not spontaneously active, while pyramidal cells in vivo fire vigorously. Stimulation of the mediodoral thalamic glutamatergic projections to the PFC result in an excitatory effect on **PFC** pyramidal cells that is reduced by DA (38). This suggests that DA exerts a modulatory role over excitatory afferents to the **PFC.** When considered in light of the fact that pyramidal cells are not spontaneously active in the slice preparation (but are spontaneously active in vivo), it appears likely that a dopaminergic inhibition of **PFC** pyramidal cells is observed only when pyramidal cells are driven by certain excitatory afferents. In other words, the electrophysiological data suggest that DA operates to modulate excitatory drive over pyramidal cells. While any of the sources of excitatory afferents to the **PFC** may he important in this regard, the neurons that contribute the excitatory component of the triadic arrangement with DA in the **PFC** may be particularly important.

In contrast to the inhibitory effect of DA on pyramidal cells, DA increases the firing rate of interneurons and increases the release of GABA from these cells in the **PFC** (39,40). The actions of DA appear to be mediated predominantly through a D_2 receptor, with a synergistic action upon D_1 stimulation (39). DA agonists elicit an increase in [^{3}H]GABA release (39) and extracellular GABA levels in the **PFC** (41); DA antagonists decrease extracellular GABA levels (42). Since GABA inhibits pyramidal cell activity, one can conceptualize DA as inhibiting pyramidal cell activity through two mechanisms: 1) directly via contacts with pyramidal cells,

and 2) indirectly by enhancing GABA release from interneurons.

STRESS-INDUCED ACTIVATION OF MESOCORTICAL DOPAMINE NEURONS

It has been almost 25 years since the discovery that stress increased the release of DA in the PFC (2). During the time since publication of that paper, the response of mesoprefrontal DA neurons to stress has been extensively investigated (2,43,44). The attention devoted to this topic has in part been due to the unusual sensitivity of the mesoprefrontal cortical DA innervation to stress. Although a large number of different stressors reliably increase DA utilization and release in the PFC of the rat, many stressors also concomitantly increase activation of other cortical neurochemical systems, including noradrenergic and serotonergic innervations. The simultaneous activation of the three monoamine systems in the PFC by stress appears to reflect primarily the intensity or duration of the stressor, since the DA innervation of the PFC can be activated by mild stressors (such as being placed in the environment of stressed conspecifics [45] or exposure to neutral stimulus previously paired with mild footshock [46–48]) that do not increase the activity of the cortical noradrenergic inputs. We will briefly review recent findings concerning the stress-induced activation of mesoprefrontal cortical neurons. Deutch and Roth (2) offer a more extensive review of earlier work on this topic. In addition, the reader is referred to Chapters 4 and 5 for recent developments related to the interactions of amino acid transmitters and dopamine, and the sensitization of forebrain DA systems to stress, respectively.

The Biochemical Responsiveness of the PFC DA Systems to Stress

Activation of the dopaminergic innervation of the PFC by stressors does not appear to reflect spillover of DA and metabolites from noradrenergic neurons (49,50), nor does the cortical DA response depend upon a stress-induced increase in corticosterone (51–53). Mild stressors appear to influence rather selectively the PFC DA innervation relative to other forebrain DA systems. Thus, a very mild footshock (e.g., 200 μA) will increase DA utilization in the PFC, but not in the nucleus accumbens or striatum, while a slightly higher foot shock (230 μA) will activate the nucleus accumbens DA innervation (43,47); there is a similar graded response with duration of restraint stress (43). The DA metabolism in the VTA (site of the DA cell bodies that project to the PFC) is also increased in response to mild stressors (45–47), as is DA metabolism in certain nuclei within the amygdala (54). Interestingly, exposure to a neutral stimulus previously paired with foot shock will activate the PFC but not nucleus accumbens DA systems if the footshock parameters are suitably mild (46,47,51), but exposure to a neutral stimulus previously paired with a higher intensity (current) foot shock will result in the activation of both the DA innervations of the PFC and nucleus accumbens (55.56).

The differential responsiveness of telencephalic DA systems to stress is mirrored by a heterogeneity of the prefrontal cortical DA innervations to stress. As just noted, the medial PFC of the rat is comprised of a number of distinct cytoarchitectonic regions. The PFC efferent~ are topographically organized both within and across the different cytoarchitectonic regions of the PFC (3). The different projections of PFC efferents subserve different functions. For example, the infralimbic cortex has more prominent projections to the hypothalamus and brainstem autonomic regions than do more dorsal PFC regions (3,57), and is thought to be involved in the early alerting to stress (58). We reasoned that stress may differentially alter DA release from axons innervating the different PFC regions, and found that exposure to a very mild footshock stressor that did not enhance DA utilization in the entire medial PFC resulted in a significant increase in DA utilization in the infralimbic part of the PFC (59,60). The DA innervations of more dorsal PFC regions such as the prelimbic cortex are less sensitive to stress, consistent with the postulated functions of different PFC regions (3).

We also found that the greater sensitivity of

the DA innervation of the infralimbic PFC to stress is mirrored by greater sensitivity of DA neuron cell bodies in VTA areas that project to the infralimbic cortex. Thus, restraint stress increased expression of the immediate-early gene c-fos (see Chapter 1) in a distinct subset of mesoprefrontal cortical DA neurons (61) located in the caudal and medial VTA nuclei that give rise to the DA innervation of the ventral PFC.

There are also differences in the degree to which DA metabolism is activated in the two hemispheres (i.e., there is a lateralization of the prefrontal cortical DA innervation to stress [62,63]). Surprisingly, this lateralized response bias can be detected using a relatively small sample size, and appears to be related to side biases in turning behavior (63). The observation that the lateralization of the PFC DA response to stress is related to side preference in motor behavior suggests that there are individual variations in the degree of responsiveness of cortical DA systems to stress; these individual differences may be determined in part by genetic factors.

The Functional Significance of Enhanced Cortical DA Release in Stress: The Acquisition of Coping

In a study of the effects of conditioned fear on PFC DA utilization (47), we paired footshock delivered through a grid floor (unconditioned stimulus, or UCS) with a neutral auditory conditioned stimulus (CS) for either 1 day or 5 days; the prefrontal cortical DA response to the presentation of the CS was then examined on either day 2 or 6, respectively. We were puzzled to note that in animals that received 5 days of CS–UCS pairings, there was no increase in PFC DA utilization in response to the CS, and a markedly depressed response to the UCS. In contrast, 1 day of CS–USC pairings led to the expected significant increase in cortical DA utilization in response to the CS alone, with a significantly greater response to the UCS (47). One clue pointing to the functional significance of these findings was the observation that rats introduced to the operant chamber on day 4 or day 5 of pairings immediately placed themselves prostrate on the grid floor. We interpreted this unusual behavior to indicate that the animals bad developed a coping strategy to the stressor. We surmised that by placing themselves across the grid floor, the rats were able to effectively reduce any high current-density shocks, which are due to an arc of current passing between the floor and a part of the body not quite apposed to the grid floor.

These data led us to suspect that the stress-elicited release of DA in the PFC was involved in the acquisition (but not expression) of a coping response to the stressor (2.64). This idea was buttressed by a series of studies by Scatton and colleagues in inbred strains of rats that exhibit markedly different responses to novel and threatening environments, the Roman Low-Avoidance (RLA) and Roman High-Avoidance (RHA) strains (65). These studies revealed that the "hypoemotional" RHA rats exhibited a stressor-induced increase in PFC DA metabolism, but that the "hyperemotional" RLA rats did not (64,66,67). Since the rats expressing the "least emotion" appeared to exhibit the greatest stressor-induced DA activation, it was concluded that "the stress-induced increase in cortical DOPAC [3,4-dihydroxyphenyl acetic acid] is unlikely to be a direct reflection of the emotional status of the animals" (66). Scatton and associates thus proposed that enhanced PFC DA function in response to stress may be reflected in heightened attention or cognitive processes to cope with the stressor (64). This fits well with our inability to detect a stress-induced increase in DA utilization in animals after chronic footshock exposure. The data from the RLA and RHA rat studies also were consistent with our suggestion that release of PFC DA was of importance in the acquisition, rather than performance, of the coping strategy. Finally, the observation that the RHA (hypoemotional) rats no longer exhibit an augmented PFC DA metabolism associated with an active avoidance task once the rats are successful in performing the task (67) is also in accord with our hypothesis.

The hypothesis that DA release in the PFC is involved in the acquisition of a coping response provides a unifying explanation for diverse findings. However, several authors have demon-

strated that cortical DA response to stress can be sensitized by prior exposure to stress (see Chapter 5). Although most of these studies examined cross-sensitization of stress and drugs of abuse (68,69), and therefore may shed some light on the choice of the drugs that PTSD patients frequently abuse, there are also reports of sensitization to the stress-induced increase in extracellular PFC DA levels after chronic stress. Rats repeatedly exposed to cold stressor exhibit a significantly greater augmentation of cortical DA levels after an acute tail-shock stressor than do rats exposed to the tail shock without previous cold-stress exposure (70). There are, to the best of our knowledge, no published data indicating sensitization of the cortical DA response to stress that have not used a novel stressor for the final (challenge) day.

We recently examined the effects of daily restraint stress on the ability of an acute restraint stress to evoke an increase in DA metabolism (71). In this study we used 30 minutes of restraint, since this stressor increases both DA and serotonin release in the PFC. Consistent with our previous work, we found that those animals restrained for the first time showed a markedly increased DA and serotonin utilization in the PFC. In contrast, rats restrained every day for 6 days and then restrained on day 7 (test day) did not display an increase in DA utilization (in fact, DA metabolism was nonsignificantly depressed), hut still evinced an increase in serotonin utilization. These data fit well with data from Scatton and colleagues, who noted that PFC DA metabolism in both RHA and RLA rats placed into a forced locomotion paradigm was decreased after chronic exposure to the same forced locomotion (66). These observations are consistent with the proposal that the function of prefrontal cortical DA release in response to stress is to participate in the acquisition of a coping response, and show that this condition is neurochemically specific.

Problems Associated with Attributing Internal States to Animals

We have interpreted certain behavioral and neurochemical changes as suggesting that the functional significance of the stress-elicited increase in PFC DA release is to contribute to the development of a coping strategy, the aim of which is to reduce immediate exposure to the stressor or dampen adverse effects upon subsequent exposure to the stressor. The difficulties and appropriateness of applying explanatory emotional concepts to nonhuman animals have long represented problems for neuroscientists in general and psychologists in particular. However, it is now widely accepted that the ability to experience internal states such as anxiety is not likely unique to humans, and thus the inability of nonhuman animals to describe their internal sensations or emotional states should not preclude the formulation of explanatory concepts linking stressors with observable biochemical, physiological, and behavioral responses. The terms "anxiety" and "coping" are a conceptual convenience to provide an explanatory link between observable experimental manipulations (e.g., the administration of a stressor) and the observable consequences or correlates of those manipulations.

The distinction between the definitions of anxiety, fear, and stress is vague. Stress (or a stress response) has been defined, for example, as "the nonspecific response of the body to any demand" (72), the biochemical/physiological responses to a stressor (73), and the "right side" of an inverted U-shaped arousal curve where the left side represents enhanced performance and the right side represents deteriorating performance (74). "Stress response" is also used by many in an interchangeable manner for fear or anxiety.

Fear and anxiety are sometimes distinguished by the presence or absence of an environmental threat. Fear is typically defined as an emotional reaction to a concrete immediate threat, in contrast to the definition of anxiety as an emotional reaction when the threat is not known or not physically present (i.e., the reaction is disproportionate to the actual threat [75,76]). Thus, although animals' behavioral manifestations of fear and anxiety are similar, the two states may be differentiated by the presence or absence of an appropriate direct stimulus (77). This leads one to the distinction that the neural substrates

of fear are unconditionally activated, whereas the neural substrates of anxiety are conditionally activated. This simply means that fear and anxiety are states that result from different activating stimuli (78), but does not indicate that different neural systems are necessarily involved in fear and anxiety.

Although it is generally accepted that animals experience fear, there is room to question whether animals experience anxiety, since the experience of anxiety, even in humans, is often inferred rather than observed (79). In humans, anxiety has been defined as an autonomically-derived state of unpleasantness that consists of heightened vigilance coupled with apprehension of impending and inevitable danger over which one will he powerless (80). Empirical support for the view that nonhuman animals experience anxiety is provided by the similar physiological and behavioral states (e.g., motor tension, autonomic hyperactivity, apprehensive expectation, vigilance, scanning) observed in both nonhuman and human animals in circumstances assumed to he anxiety inducing (79). Moreover, anxiolytic drugs such as diazepam inhibit normal stressor-induced behavior in rats and other nonhuman animals (81). While these arguments are somewhat circular, the converging data are consistent with the observations that the physiological sequelae of exposure to a fear-provoking state in man (such as electrical shock) and to conditioned stimuli for the actual event (such as a neutral tone) are comparable in human and nonhuman animals. To those interested in the question of operationally defining anxiety in nonhuman species, it appears that the ability to distinguish man from nonhuman animals may be most suitably made on the basis of assuming that only humans can experience anxiety.

A NEUROBIOLOGICAL MODEL OF THE STRESS-INDUCED ACTIVATION OF MESOPREFRONTAL CORTICAL DOPAMINE NEURONS

We have previously emphasized that the release of DA in the PFC in response to a stressor represents an increase in the firing rate of mesoprefrontal cortical DA neurons (2). This argument was based in part on two different types of evidence: 1) several different pharmacological manipulations of the DA cell bodies in the ventral midbrain attenuate the stress-elicited increase in DA metabolism and release in the PFC (see 2,16) and 2) stress-induced metabolic activation of A10 DA neurons in the VTA is not observed when one transplants VTA neurons to a forebrain site (82). The findings again suggest that the effects of stress are due to afferents impinging on A10 DA neurons that increase the firing rate of these cells, rather than operating through a presynaptic impulse-independent regulation of DA release in the PFC.

A recent study reported that local infusion of an AMPA family excitatory amino acid receptor antagonist into the PFC blocked the stress-elicited increase in cortical extracellular DA levels (83). These data were interpreted to indicate that the stress-elicited increase in cortical DA release was mediated locally through presynaptic influences over DA axons. An alternative explanation for these data, however, focuses on the fact that there are both glutamatergic afferents to the PFC and glutamatergic efferents from the PFC. Thus, blocking an excitatory glutamatergic input onto pyramidal cells prevents the activation of a long-loop excitatory influence of the PFC over mesoprefrontal cortical DA somata in the VTA. Accordingly, if the stress-elicited increase in prefrontal cortical DA release functions in the acquisition of a coping response to stress (2,64), then the enhanced DA tone in the PFC can be assumed to dampen some stress-induced event.

We propose that glutamatergic afferents to the PFC exert an excitatory influence over pyramidal neurons. Some of these pyramidal cells project to the VTA (84), where they drive mesoprefrontal cortical DA neurons. In turn, the release of DA in the PFC dampens the excitatory input onto the pyramidal cell. This scheme takes into account several findings: 1) stress increases glutamate release in the PFC (85.86); 2) both DA axons and nondopaminergic excitatory inputs synapse with PFC pyramidal neurons (the triadic arrangement [21] discussed earlier); and 3) electrophysiological data indicate that DA modu-

lates the excitatory drive exerted upon pyramidal cells by excitatory amino acid inputs (38). Finally, the model that we propose is consistent with a large body of data indicating that the stress-induced increase in DA tone in the PFC depends upon the presence of intact afferents to the somatodendritic areas of the midbrain DA neurons (2,16); among these afferents may be the glutamate-containingprojections originating in the PFC.

This model is testable, since it hinges on identification of the excitatory input to the pyramidal cell that is located in proximity to the DA terminal. Thus, one should be able to lesion the relevant excitatory input(s) to the PFC and thus block the stress-elicited activation of DA afferents to the PFC. Although there are several possible sites of origin for these afferents (including certain medial thalamic nuclei, the basolateral amygdala, CA1 neurons of the hippocampus, other cortical sites, the basal forebrain, or even nondopaminergic neurons in the VTA), perhaps the most likely source for this critical excitatory input is the area that contributes to the triadic arrangement with the pyramidal cell and a DA input. A recent report suggests that the hippocampus is not the source of the excitatory input that contributes to the triadic arrangement (31).

Among the most likely candidatesfor the critical excitatory input to the PFC is the basolateral amygdala. In the rat there are extensive projections from the basolateral nucleus onto the medial PFC (29,87,88); projections to different parts of the PFC are derived from the anterior and posterior basolateral nucleus, with the more posterior division innervating the infralimbic and ventral prelimbic PFC (88). Both direct and indirect evidence are consistent with the speculation that the activation of glutamatergic amygdala inputs to the PFC are the proximate cause of a compensatory increase in cortical DA release. Direct evidence is provided by the recent observation that excitotoxic lesions of the basolateral amygdala prevent the stress-induced increase in PFC DA metabolism and release (55,56). Less direct but consistent with the model is the key role that the amygdala plays in determining the emotional salience of stressors (see Chapters 7 and 11). Finally, lesions of the PFC do not alter the acquisition of a conditioned emotional response (CER) but delay extinction of the CER (89; see Chapter 7).

We propose tbat the amygdaloid inputs to the PFC may be a critical source of afferent drive to the PFC pyramidal cell that is activated by stress. In turn, excitatory glutamatergic efferents from the PFC to the A10 DA neurons increase the firing rate of mesoprefrontal cortical neurons, which finally dampens the cortical output. Since neurons in the PFC project to the basolateral amygdala as well as VTA (3), it is also possible that the PFC projection neurons contacted by DA afferents directly dampen a positive feedback loop originating in the amygdala.

We have emphasized the amygdala in this loop because of the obvious relevance of the amygdala to fear and stress (see Chapters 7 and 11). However, it is possible, if not likely, tbat there are multiple sources of excitatory drive to the PFC that are important. Particularly interesting in this regard would be projections to the PFC from the thalamic paraventricular nucleus and the mediodorsal thalamic nucleus (90.91).

Most of the data upon which we have based our model of the stress-elicited activation of the PFC DA innervation was obtained from studies of rats. However, there are key differences between rodent and primate species. Among the anatomical differences is the fact that the amygdala of primates projects to orbital prefrontal and anterior cingulate cortices, but does not innervate the dorsolateral prefrontal cortex (12). This observation suggests tbat our model (at least with regard to the amygdala component) is consistent with the orbital cortex being the critical cortical site in primate species. The medial PFC of the rat is comprised of several distinct cytoarchitectonic regions that are thought to correspond to spatially-segregated prefrontal cortical regions in primates. As just noted, the ventral PFC (infralimbic cortex) of the rat is the region of the PFC in which the DA response to stress is most vigorous (59) and is the area of the PFC that has direct autonomic projections (57). This ventral portion of the rodent PFC is thought to he homologous to the orbital cortex in primates. Thus, our model is applicable to primates and rodents, and emphasizes in particu-

lar those extended circuits formed with the orbital PFC.

RELEVANCE OF THE PREFRONTAL CORTICAL DOPAMINE SYSTEMS TO PTSD

Systematic study of the neurohiology of PTSD is only beginning. We hope that we have provided a useful organizational framework for explaining the activation of the prefrontal cortical DA system that may he of value to scientists studying stress. We have also tried to pose several questions that scientists embarking on clinical studies may find provocative.

We have presented a model to explain the mechanisms that govern stress-induced activation of the prefrontal cortical DA system. It may be useful to conceptualize, at least as a starting point for new investigations, the development of PTSD in terms of the neurohiology and functional significance of the stress-elicited increase in PFC DA release.

We proposed that the functional significance of stress-elicited DA release in the PFC lies in the acquisition of coping strategies. This would suggest that some functional defect in cortical DA systems in PTSD patients would lead to an inability to develop an effective coping strategy for dealing with trauma; this failure would subsequently render the person more susceptible to contextual stimuli associated with the stressor. In the face of repeated exposure to stimuli associated with the original stressor, the inability to develop a coping strategy would result in stimulus generalization, and thus acontinued susceptibility to flashbacks.

The hypothesis that there is a functional defect in orbital cortical DA function in PTSD may explain several characteristics of PTSD patients. These patients are hypervigilant and frequently paranoid. Such behaviors, however, suggest a hyperdopaminergic condition in PTSD patients, miming counter to the defect in functional cortical DA tone that we propose. Recent theories of the pathogenesis of schizophrenia have had to deal with a similar paradox, and have led to the hypothesis that cortical dopaminergic hypofunction results in a transsynaptic increase in DA tone in suhcortical sites and the generation of positive symptoms (92–94). Studies in animals have documented that depletions of prefrontal cortical DA increase suhcortical DA tone under challenge conditions (94–96). It is important to note that lesions of the PFC DA innervation do not increase subcortical DA tone under basal conditions (94), but only under challenge conditions, such as stress. In other words, even in the presence of a greater than 80% decrease in cortical DA levels there remains sufficient dopaminergic tone to maintain adequate inhibition of cortical outflow neurons under basal conditions; the defect becomes manifested under conditions of demand, such as stress or associated stimuli. This fits well with current conceptions of PTSD. We hasten to add that we are advancing the possibility of a functional DA defect in the orbital cortex, which may in turn enhance subcortical DA function. However, we do not suggest that F'TSD and schizophrenia are related. Although there may be orbital cortical dysfunction in schizophrenia (and thus the emergence of stress-induced exacerbation of the psychotic process), it appears likely that there is a functional alteration in the dopaminergic innervations of other cortical regions, including the dorsolateral PFC and perhaps medial temporal lobe structures.

A functional deficit in cortical DA tone would also explain the apparently poor response of PTSD patients to neuroleptic drugs (see Chapter 26), which are DA receptor antagonists. However, controlled studies of this issue are lacking. Interestingly, clozapine differs from typical antipsychotic drugs by virtue of its actions on the PFC (97–101), including the observation that it sharply increases extracellular DA levels (98,99). It would therefore be interesting to know if clozapine is useful in the treatment of PTSD.

Although one can develop arguments that are consistent with a hypothesis of a defect in cortical DA tone in PTSD, what data can he marshaled in direct support of the hypothesis? Unfortunately, there are no direct data. A few studies have examined peripheral indices of DA function in F'TSD, including reports document-

ing a change in 24-hour urinary homovanillic acid (HVA) and DA levels (102,103). However, peripheral measures of DA function are notoriously poor indices of changes in central DA systems, and as such do not provide any useful test of our hypothesis. Clearly, studies aimed at determining functional alterations in central DA systems would be most useful. In the absence of methods to measure directly cortical DA function in man, useful alternative strategies might include examination of CSF HVA levels in PTSD patients, since studies of nonhuman primates indicate that CSF HVA levels correlate with DA concentration in the dorsolateral PFC but not in any other region (104). At the current time, PET and SPECT in vivo imaging methods do not have the requisite sensitivity to detect either fluoro-DOPA or DA transporter signals from the cortex.

However, in vivo functional studies of cortical regions (including the orbital cortex) are possible with fluoro-deoxyglucose or using methods that detect changes in blood flow. Again, we are aware of no such studies in PTSD. Interestingly, studies of co-morbid psychiatric conditions with PTSD reveals significant association with obsessive-compulsive disorders (OCD) (see Chapter 24); imaging studies in OCD have revealed changes in metabolic activity in the orbital cortex and allied striatal regions (105,106).

We have put forth a hypothesis of the pathophysiology of PTSD that focuses on the prefrontal cortex, and specifically directs attention to the orbital cortex. We have focused on dopamine systems because of the striking effects of stress on central DA systems. We wish to note, however, that other monoamines in the cortex also exert inhibitory effects over cortical projection neurons, either directly or indirectly (40). Cortical norepinephrine release is increased by stress (see chapter 3), as is serotonin release (107–109). Although these monoaminergic transmitters in the PFC are not as sensitive to the effects of stress as the mesoprefrontal cortical DA system, they may function cooperatively in the scheme that we have outlined to influence cortical projections, including those to brainstem monoaminergic cell group regions and the amygdala. Indeed, in view of the myriad changes in transmitter systems that have been observed in PTSD, it seems likely that the central pathology involves more than one transmitter system.

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